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UNITED STATES DISTRICT COURT
DISTRICT OF UTAH

NUTRACEUTICAL CORPORATION and SOLARAY, INC.,	)	
Plaintiffs,	)	
v.	)	Case No. 2:04CV00409 TC
LESTER CRAWFORD, D.V.M., Acting Commissioner, U.S. Food and Drug Administration, et al.,	)	
Defendants.	)	

DEFENDANTS' OPPOSITION TO PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT, AND MEMORANDUM IN SUPPORT OF CROSS-MOTION FOR SUMMARY JUDGMENT

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I. INTRODUCTION

Plaintiffs ("Nutraceutical")[1] challenge the validity of the Food and Drug Administration's ("FDA" or "agency") regulation (Final Rule)[2] to ban the distribution of ephedrine alkaloid-containing dietary supplements ("EDS"). Nutraceutical alleges in its complaint that the Final Rule violates the Dietary Supplement Health and Education Act of 1994 ("DSHEA")[3] and the Administrative Procedure Act ("APA"). Nutraceutical seeks to enjoin FDA from enforcing the Final Rule against its Ephedra product (Nutraceutical's "product"), which it alleges contains 10 milligrams ("mg") or less of ephedrine alkaloids per daily dose. In the alternative, Nutraceutical claims that the Final Rule is a taking of its property in violation of the Fifth Amendment, entitling it to compensatory damages.

On August 18, 2004, Nutraceutical filed a Motion for Summary Judgment. Nutraceutical argues that:

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[1] The term "Nutraceutical" as used herein refers to Plaintiffs collectively or Nutraceutical Corporation or Solaray, Inc., individually.

[2] Final Rule Declaring Dietary Supplements Containing Ephedrine Alkaloids Adulterated Because They Present an Unreasonable Risk, 69 Fed. Reg. 6788 (Feb. 11, 2004); see Administrative Record ("A.R.") at 105594-855. For convenience, citations are provided to the Federal Register, when applicable, rather than the administrative record. Citations to reference numbers ("Ref.") correspond to the documents referenced in the Final Rule and listed in section XII of the Rule. 69 Fed. Reg. at 6849-53. All of the references in the Final Rule are contained in the administrative record. References cited herein are attached at Exhibit I.

[3] Pub. L. No. 103-417, 108 Stat. 4325 (1994), amending the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301 et seq.

(1) FDA failed to meet its burden under DSHEA and the APA to show that EDS, such as Nutraceutical's product, containing 10 mg or less of ephedrine alkaloids per daily dose present an unreasonable risk of illness or injury;

(2) FDA's risk-benefit analysis to determine "unreasonable risk" is an impermissible interpretation of DSHEA;

(3) FDA's alleged differential treatment of EDS and conventional foods violates DSHEA and the APA; and

(4) FDA violated the APA's notice-and-comment rulemaking requirements in promulgating the Final Rule.

First, FDA has satisfied its burden of proving unreasonable risk under DSHEA and the APA. The administrative record establishes that all EDS, including dietary supplements containing 10 mg or less of ephedrine alkaloids per daily dose, are adulterated because they present an unreasonable risk of illness or injury. FDA has determined that a safe dose of ephedrine alkaloids in dietary supplements cannot be identified. Because the benefits of EDS are so minimal at all doses, the risks of the products, regardless of dose, outweigh the potential benefits. DSHEA does not require FDA to make dose-specific findings for certain EDS where, as here, the evidence shows that all EDS present an unreasonable risk.

Second, the plain meaning of "unreasonable risk" requires a comparison of the risks and benefits of a product, i.e., a risk-benefit analysis. Even if the statute were considered ambiguous,

FDA's interpretation of "unreasonable risk" is not only permissible, but the most reasonable and plausible construction of DSHEA, 21 U.S.C. § 342(f)(1)(A).

Third, regulating EDS differently from conventional foods does not create a violation of DSHEA or the APA. In the Federal Food, Drug, and Cosmetic Act ("FDCA"), Congress has mandated certain differences in the regulatory schemes for dietary supplements and foods. Thus, to the extent that FDA regulates EDS differently from conventional foods, such difference is appropriate and compelled by statute.

Fourth, FDA followed the rulemaking procedures required under the APA and FDA regulations. FDA's decision to declare all EDS adulterated because they present an unreasonable risk of illness or injury is fairly foreshadowed in the proposed rule, subsequent notices, and comments advanced during the rulemaking. In addition, the risk-benefit analysis used to determine unreasonable risk in the Final Rule is not a separate substantive rule and did not require a separate notice-and-comment rulemaking.

Finally, the Final Rule does not constitute an unconstitutional taking, and Nutraceutical is not entitled to any compensation from the government.

Nutraceutical is not entitled to any of the relief it seeks. The Court should deny Plaintiffs' Motion for Summary Judgment and grant Defendants' Cross-Motion for Summary Judgment.

II. REGULATORY FRAMEWORK

Ephedrine alkaloids used as ingredients in dietary supplements are naturally occurring, amphetamine-like, stimulant compounds derived from plants and plant extracts.[4] EDS have been widely promoted to achieve weight loss, enhance athletic performance, and boost energy. After an extensive review of the known pharmacology, peer-reviewed scientific literature, and adverse event reports ("AERs") concerning EDS, FDA concluded that the benefits associated with these products were minimal and that the risks of illness or injury were substantial. Therefore, using a risk-benefit analysis, FDA determined that the products pose an "unreasonable risk of illness or injury."

A. THE DIETARY SUPPLEMENT HEALTH AND EDUCATION ACT OF 1994

Pursuant to DSHEA, dietary supplements are regulated as a subset of foods unless they make disease claims that bring them within the drug definition. See 21 U.S.C. § 321(ff), (g)(1); cf. 21 U.S.C. § 343(r)(6). Accordingly, with few exceptions not relevant here, dietary supplement manufacturers are not required to provide evidence of product safety and efficacy to FDA prior to marketing their products. DSHEA also does not require dietary supplement manufacturers to comply with post-market product safety monitoring or reporting requirements that the FDCA requires for drugs. Therefore, FDA must rely on voluntary studies, voluntarily reported adverse event reports, and other data to identify potential safety problems with dietary supplements.

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[4] Ephedrine alkaloids can also be synthetically derived.

Under DSHEA, a dietary supplement is adulterated if it presents a "significant or unreasonable risk of illness or injury."[5] See 21 U.S.C. § 342(f)(1)(A). FDA interpreted the "unreasonable risk" standard, which Congress did not define in the statute or the legislative history, to require a risk-benefit analysis. See 69 Fed. Reg. at 6797. DSHEA places the burden on FDA to demonstrate that EDS present an unreasonable risk of illness or injury.[6]

B. FDA'S RULEMAKING

On February 11, 2004, after undertaking notice-and-comment rulemaking in accordance with the APA, FDA published the Final Rule declaring EDS adulterated under DSHEA and not legally marketable in the United States. The Final Rule became effective on April 12, 2004.

The Final Rule was the culmination of a long process beginning in the early 1990s when FDA began receiving AERs reflecting illnesses and injuries associated with the use of EDS. After marshaling and reviewing the then-available evidence regarding the public health and safety risks associated with these products, FDA published a proposed rule in 1997. Following a partial withdrawal of the proposed rule in 2000, FDA evaluated additional evidence and scientific studies and reopened the comment period three times. Thereafter, the Final Rule,

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[5] Here, FDA proceeded under the "unreasonable risk" standard and did not consider whether EDS present a "significant risk." See 69 Fed. Reg. at 6793.

[6] If challenged, the agency's determination is subject under DSHEA to de novo review. See 21 U.S.C. § 342(f)(1) ("In any proceeding under this subparagraph, the United States shall bear the burden of proof on each element to show that a dietary supplement is adulterated. The court shall decide any issue under this paragraph on a de novo basis.").

published in February 2004, concluded that EDS are adulterated under 21 U.S.C. § 342(f)(1)(A)[7] because, when their minimal benefits – the most significant of which is modest, short-term weight loss – are weighed against their substantial risks – heart attack, stroke, and death – they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or, if no conditions of use are recommended or suggested in labeling, under ordinary conditions of use. See 69 Fed. Reg. at 6788-89.

The administrative record, comprising over 133,000 pages, contains the scientific data, expert reviews, comments submitted by interested persons, including Nutraceutical, and other materials that FDA considered in making its decision. FDA considered evidence from three principal sources: (1) the well-known, scientifically established pharmacology of ephedrine alkaloids; (2) peer-reviewed scientific literature on the effects of ephedrine alkaloids; and (3) adverse events (including published case reports) reported to have occurred following consumption of EDS. 69 Fed. Reg. at 6788, 6798, 6800-11, 6814-22. FDA commissioned expert reviews of the scientific evidence and assessed the findings of the expert reviews. Id. at 6802, 6805, 6814. In addition, FDA reviewed each of the thousands of comments submitted to

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[7] In pertinent part, the statute provides:

> A food shall be deemed to be adulterated –
>
> * * *
>
> (f)(1) If it is a dietary supplement or contains a dietary ingredient that –
> (A) presents a significant or unreasonable risk of illness or injury under –
> (i) conditions of use recommended or suggested in labeling, or
> (ii) if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use.

the agency. See id. at 6792-93. The agency concluded that all EDS pose an unreasonable risk of illness or injury and, acting under DSHEA and other provisions of the FDCA, banned further distribution of EDS to protect the public health. See id. at 6796, 6799, 6825-27.

III. STATEMENT OF UNCONTESTED MATERIAL FACTS

A. THE 1997 PROPOSED RULE

1. In 1993, FDA began receiving AERs reflecting illnesses and injuries associated with the use of EDS. In response to the growing number of AERs and the absence of publicly available safety data on EDS, FDA convened its Food Advisory Committee and an ad hoc working group (collectively, the "committee") to advise the agency how to address the rising health concerns associated with these dietary supplements. See 62 Fed. Reg. 30678, 30680 (June 4, 1997). After reviewing the then-available evidence regarding the pharmacology of EDS, scientific literature, and AERs, the committee concluded that EDS may cause serious adverse events and recommended that FDA take regulatory action to address the public health and safety risks associated with these products. See id. at 30691.

2. In June 1997, FDA published a proposed rule on EDS. See 62 Fed. Reg. 30678. The rule proposed to find that an EDS product is adulterated if it contains 8 mg or more of ephedrine alkaloids per serving, or if its labeling suggests or recommends conditions of use that would result in an intake of 8 mg or more during a 6-hour period or a total daily intake of 24 mg or more of ephedrine alkaloids. Id. In addition, the rule proposed to: (1) prohibit EDS labeling claims for uses that require long-term intake to achieve the purported effect; (2) prohibit EDS

from combining sources of ephedrine alkaloids with other stimulant ingredients, such as caffeine; (3) require EDS warning statements alerting consumers to possible drug interactions, directing them not to take the product for more than 7 days, and advising certain consumers (e.g., pregnant and nursing women and individuals with certain diseases) (a) to consult a health care provider before use, and (b) to stop use and contact a health care professional if they develop certain signs or symptoms; and (4) require that claims that encourage short-term excessive intake be accompanied by a statement that taking more than the recommended serving may result in serious adverse health effects. See id. at 30691-704.

3. After FDA issued the 1997 proposed rule, the House Committee on Science requested that the Government Accounting Office ("GAO") examine the scientific bases for FDA's proposed requirements. On August 4, 1999, GAO released its report entitled "Dietary Supplements: Uncertainties in Analyses Underlying FDA's Proposed Rule on Ephedrine Alkaloids." 65 Fed. Reg. 17474 (April 3, 2000). GAO concluded that FDA was justified in determining that the number of AERs relating to EDS warranted the agency's attention and consideration of steps to address safety issues, but recommended that FDA "provide stronger evidence on the relationship between the intake of [EDS] and the occurrence of adverse reactions that support the proposed dosing level and duration of use limits." Id. at 17475. In light of GAO's conclusions and other comments to the proposed rule, on April 3, 2000, FDA withdrew the proposed restrictions on dosage and directions for frequency of use, the proposed prohibition on labeling claims for uses that encourage long-term intake, and the proposed warnings advising

consumers not to exceed the recommended servings or use the product for more than 7 days, but maintained the other warning statement proposals and the proposed prohibition on combining EDS with other stimulant ingredients. See id. at 17475-76.

4. On March 5, 2003, FDA issued a Federal Register notice reopening the comment period for the 1997 proposed rule. See 68 Fed. Reg. 10417 (March 5, 2003). In this notice, FDA requested public comment on additional evidence and scientific studies that it had received after the publication of the 1997 proposed rule. The notice also stated that FDA intended to consider whether "FDA should determine that [EDS] present a 'significant or unreasonable risk of illness or injury'" and sought comments on that issue. See id. at 10419 (quoting 21 U.S.C. § 342(f)(1)(A)).

B. THE 2004 FINAL RULE

5. FDA published its Final Rule on February 11, 2004, concluding that EDS are adulterated under 21 U.S.C. § 342(f)(1)(A) because, when their minimal benefits are weighed against their substantial risks, they present an unreasonable risk of illness or injury under the conditions of use recommended or suggested in labeling, or, if no conditions of use are suggested or recommended in labeling, under ordinary conditions of use. See 69 Fed. Reg. at 6788. Because FDA found that the use of EDS does not provide a benefit sufficient to outweigh the increased risk of heart attack, stroke, and death, the agency concluded that all such products pose an unreasonable risk. Id. at 6789.

C. FDA'S FINDINGS – BENEFITS

6. FDA evaluated EDS used for weight loss, enhancement of athletic performance, increased energy, eased breathing, and similar uses. 69 Fed. Reg. at 6818-22. With regard to claims of being "energized" or "more alert," FDA concluded that these effects may be of modest benefit to the individual (if they occur at all), are temporary, and do not improve health. Id. at 6822, 6826. FDA also concluded that there are no data to support an "eased breathing" benefit from EDS use in healthy people. Id. In addition, FDA concluded that there is no evidence to indicate that ephedrine alone enhances athletic performance. Id. at 6821-22, 6826. FDA found that the reported effect was only for synthetic ephedrine and caffeine in combination, and was modest and very short term. Id. Moreover, FDA found no evidence that botanical ephedrine alkaloids enhanced athletic performance. Id.

7. FDA determined that the "best" clinical evidence for a benefit from EDS is for weight loss, but that the evidence supports only a modest short-term weight loss (up to 6 months). 69 Fed. Reg. at 6789, 6818-21, 6825-26. FDA further concluded: (1) that there are no scientific data to show that short-term weight loss results in improved health outcomes; (2) that weight loss achieved with botanical ephedrine alkaloids is insufficient to have a positive effect on cardiovascular risk factors or health conditions associated with being overweight or obese; (3) that only long-term weight loss in overweight or obese individuals has been shown to reduce the risk of morbidity and mortality; and (4) that there are no appropriate, well-designed studies showing that EDS produce long-term weight loss (i.e., weight loss for more than 6 months). Id.

8. FDA found that the RAND report provides the most comprehensive review of efficacy studies for ephedrine alkaloid containing products with claims for weight loss. 69 Fed. Reg. at 6818-19, 6826 and Refs. 21, 22. The RAND report is a review conducted by the Southern California Evidence Based Practice Center and commissioned by the National Institutes of Health. As explained in the preamble to the Final Rule, the RAND report found evidence that supported an association between short-term use of synthetic ephedrine, synthetic ephedrine plus caffeine, or dietary supplements that contain botanical ephedrine alkaloids with or without botanicals containing caffeine, and a statistically significant increase in short-term weight loss compared to placebo. Id. The RAND report concluded that products containing ephedrine alkaloids in combination with caffeine resulted in a modest weight loss of approximately 2 pounds per month more than placebo over a period of 4 to 6 months. Id. RAND concluded that the use of ephedrine without caffeine was associated with a statistically significant increase in weight loss (1.3 pounds of weight loss per month) compared with that of placebo for up to 4 months of use. Id. RAND identified a single trial of 3 months duration that assessed the effect of herbal ephedra versus placebo. Id. Those in the ephedra group lost 1.8 pounds more per month than did those in the placebo group. Id.

9. FDA noted that, from a health perspective, the goal of weight loss is to prevent the morbidity and mortality associated with overweight and obesity. 69 Fed. Reg. at 6819 and Refs. 66, 129, 130. FDA found that, although the improvements in obesity/overweight and the accompanying risk factors may be demonstrated in as few as 1 to 2 months, the improvements

must be maintained for years to achieve a reduction in risk of conditions associated with obesity, such as hypertension, high cholesterol, and insulin resistance with glucose intolerance. Id. at 6819 and Refs. 66, 126, 127, 128. FDA concluded, therefore, that interventions necessary for successful weight maintenance must be long-term. Id. at 6819. FDA found no evidence that demonstrates long-term weight loss with EDS. Id.

D. FDA'S FINDINGS – RISKS

Overview

10. FDA found that people who use EDS are at increased risk of serious adverse events, including heart attacks, stroke, and death. 69 Fed. Reg. at 6789, 6800-04, 6825. More specifically, FDA found: (1) susceptible individuals (e.g., those with coronary artery disease or heart failure), many of whom may not know they have these underlying illnesses, are at increased risk of adverse health effects because EDS can cause cardiac arrhythmias (abnormal heart rhythms), even when the product is ingested at recommended doses over a short course (one or a few doses); (2) over longer periods of EDS use, the risk of adverse health effects to the general population, including but not limited to susceptible individuals, increases because of a sustained elevation in blood pressure; and (3) the risk of harmful consequences from elevated blood pressure increases the longer the blood pressure remains high, and such adverse health effects are likely to occur sooner in individuals with hypertension (many of whom are likely unaware that they have hypertension). Id. at 6802, 6825.

Pharmacological Effects of Ephedrine Alkaloids

11. Ephedrine alkaloids belong to a family of compounds called sympathomimetics, which raise blood pressure. 69 Fed. Reg. at 6801, 6802. Sympathomimetics mimic the effects of epinephrine and norepinephrine, which occur naturally in the body. Id. Sympathomimetics increase blood pressure and heart rate by binding to certain receptors in the body, including those present in the heart and blood vessels. Id. at 6801 and Refs. 35, 36, 37, 41. They also stimulate the release of norepinephrine, which further increases the sympathomimetic effects of these compounds. Id.

12. FDA's evaluation of the scientific literature revealed that long-term use of sympathomimetics results in a sustained increase in blood pressure, which increases the risk of stroke, heart attack, and death, even in people with "normal" blood pressure. See 69 Fed. Reg. at 6801-02. FDA's evaluation also revealed that, in susceptible individuals, even short-term use of sympathomimetics can induce cardiac arrhythmias in people with underlying coronary artery disease and cause increased mortality in people with congestive heart failure. See id.

13. FDA found that ephedrine alkaloids in dietary supplements have the same or similar effects as other sympathomimetics on heart rate and blood pressure. 69 Fed. Reg. at 6801. In particular, the results of the Boozer et al. (2002) study (hereafter "Boozer study") added significantly to the evidence demonstrating to FDA that EDS are associated with unreasonable safety risks. Id. at 6791.

Long-Term Use of EDS

14. FDA reviewed controlled clinical trials using products containing ephedrine alkaloids. The results of these trials confirm the products' sympathomimetic effects. 69 Fed. Reg. at 6801. FDA evaluated single-dose studies of EDS, which showed that these products cause increases in both heart rate and blood pressure in healthy subjects. Id. and Refs. 42, 43, 44. FDA also evaluated the Boozer study, a multiple-dose study, which the agency found clearly demonstrated a higher blood pressure measurement after one month of continued exposure to EDS plus caffeine compared with placebo. Id. at 6801 and Ref. 49.

15. The Boozer study examined the effects of a combination of ephedrine alkaloids (from Ephedra) and caffeine (from kola nut) compared with placebo over a six-month period in a highly selected population of obese and overweight individuals, who were carefully screened by medical history and medical evaluation to eliminate cardiovascular and other acute or chronic disorders. 69 Fed. Reg. at 6801. As FDA described in the preamble to the Final Rule, the study measured sitting blood pressure in the clinic using the cuff method for all 6 months (at weeks 1, 2, 3, 4, and every 4 weeks thereafter) of the study. Id. The study also measured changes in blood pressure throughout the day (i.e., over a 24-hour period) at weeks 1, 2 and 4 using an automated blood pressure monitoring ("ABPM") device, a method that provides more frequent measurements of blood pressure and is, therefore, better able to evaluate blood pressure effects over time. Id.

16. The Boozer study found that the ephedrine alkaloid/caffeine-treated subjects showed statistically significant higher average blood pressure measurements over a 24- hour period at week 4 as measured by ABPM (approximately 4 mm Hg for both systolic and diastolic blood pressure) as compared to placebo-treated subjects. 69 Fed. Reg. at 6801. (Systolic blood pressure is the maximum pressure and diastolic blood pressure is the minimum pressure; both are measured in millimeters of mercury ("mm Hg").) FDA concluded that, because small changes from baseline can occur for a wide variety of reasons and are commonly observed in both placebo-treated subjects and subjects treated with a test substance, the ABPM data are important because they demonstrate that the effect of EDS on blood pressure is not transient, but is evident after 1 month of continued exposure (when measured by ABPM) and, therefore, would be expected to persist long-term. Id. at 6802. FDA also determined that the effect reported in this study cannot be attributed to the caffeine because the effect of caffeine on blood pressure is transient and disappears within 2 weeks of continued use. Id. at 6801, 6802 and Refs. 45 and 46.

17. Scientific data clearly show that a sustained increase in blood pressure increases the risk of cardiovascular disease, and that an increase in blood pressure in any population, even individuals with "normal" blood pressure, will increase the risk of heart attack, stroke, and death in that population. 69 Fed. Reg. at 6801, 6802, and Refs. 29, 29a, 54. FDA also found that epidemiological studies support a graded and continuous relationship between increased blood pressure and risk of stroke, heart attack, and sudden death, even when the increase is within the normal range. Id. at 6802 and Refs. 29, 30. FDA therefore concluded that a dietary supplement

that caused a sustained rise in blood pressure across the population would increase the risk of cardiovascular events, including stroke, heart attack, or death, and that many people would be at an increased risk with long-term use of EDS. Id. at 6798-99, 6802.

Short-Term Use of EDS

18. FDA found that, with short-term use of EDS, people with congestive heart failure are at greater risk of death. 69 Fed. Reg. at 6801, 6802. FDA reviewed studies observing increased mortality in people with congestive heart failure who were treated with sympathomimetic drugs or drugs that increase the effect of certain types of sympathomimetics. Id. and Refs. 38, 39, 40, 59, 60, 61. FDA noted that the increase in mortality (from heart failure and sudden death) was seen in relatively short-term studies. Id.

19. FDA found that, with short-term use of EDS, people with coronary artery disease may experience a worsening of the disease due to cardiac arrhythmias. 69 Fed. Reg. at 6802. FDA reviewed studies documenting that people with coronary artery disease are more susceptible to the well-known pro-arrhythmic effects of sympathomimetics. Id. and Refs. 62, 63, 64. FDA noted that the occurrence of such an arrhythmic event does not require prolonged use but represents a risk associated with each use, including the first. Id.

20. FDA noted additional factors that complicate the risk of adverse health effects from short-term use of EDS in susceptible populations (e.g., individuals with coronary artery disease or heart failure). First, FDA found that people are commonly unaware of their susceptibility. Congestive heart failure and coronary artery disease may not cause prominent

symptoms until later in the course of these conditions and, therefore, individuals in these susceptible groups may be unaware of their compromised health status. 69 Fed. Reg. at 6802. As a consequence, such individuals may not know that they are at an increased risk for developing significant cardiovascular adverse events from short-term use of EDS and therefore would not know to avoid these products. See id. Second, overweight and obese individuals are particularly prone to hypertension, coronary artery disease, and/or heart failure. Id. and Refs. 65, 66. Overweight and obese people are among the groups most likely to consume EDS because EDS are marketed for weight loss. FDA found that studies of hypertension treatments suggest that the increase in risk normally associated with long-term use of EDS would occur fairly quickly in hypertensive individuals. Id. at 6802 and Refs. 29, 30, 55, 57, 58. Because overweight and obese people are more likely to have conditions (i.e., coronary artery disease and heart failure) that place them in susceptible groups or to experience adverse health effects sooner as a result of hypertension, FDA concluded that the overweight and obese population is at a greater risk from short-term use of sympathomimetics. Id. at 6802.

21. Like individuals with coronary artery disease or heart failure, individuals with hypertension also may be unaware they have this condition and therefore would not know that they are at increased risk for developing significant cardiovascular adverse events from EDS use. See 69 Fed. Reg. at 6802. Approximately one in four adults has high blood pressure; of those with high blood pressure, 31 percent are not aware that they have it. Id. and Ref. 53. The extremely high prevalence of diagnosed and undiagnosed hypertension in the U.S. population

and the likelihood that blood pressure in obese patients is already elevated increased FDA's concern as to the 4 mm Hg effect shown by the Boozer study. Id. at 6802.

AERs

22. FDA also found that the AERs corroborate the scientifically established pharmacology documenting the health risks associated with EDS. 69 Fed. Reg. at 6814-15. FDA received more than 3,000 AERs submitted directly to the agency plus approximately 16,000 reports from call records submitted by Metabolife International, one of the largest distributors of EDS. Id. at 6814. FDA, and others, have reviewed and analyzed the AERs in depth to add to the body of evidence and to assure that all relevant evidence is considered. Id. and Refs. 109-115. Despite the inherent limitations of such reports, FDA's detailed review of the AERs submitted to the agency for EDS and comparison of those AERs with scientific data about the pharmacology of these substances established that the AERs are consistent with the known and expected pharmacological effects of these products. Id. at 6814-15 and Refs. 109, 115, 116.

IV. RESPONSE TO NUTRACEUTICAL'S STATEMENT OF UNCONTESTED MATERIAL FACTS

Defendants have no objection to the statements of fact contained in paragraphs 2, 3, 11, 12, 13, 14, 16, and 24 of the Memorandum of Points and Authorities in Support of Plaintiff's Motion for Summary Judgment. Although Defendants do not agree with statements made in the remaining paragraphs, these objections do not raise a triable issue of fact because the objections involve allegations of immaterial facts, allegations of material facts that cannot be genuinely

disputed, issues of law, or, in one instance, a typographical error. However, Defendants make the following objections for the record:

1. The allegations in paragraph 1 are denied to the extent that they suggest that the Ephedra genus of plants has been used as a conventional food for thousands of years. As stated in the Final Rule, several Ephedra species have a long history of use in traditional Asian medicine. 69 Fed. Reg. at 6793-94.

4. The allegations in paragraph 4 are denied. Ephedrine is typically the predominant alkaloid in the raw material of most ephedrine alkaloid-containing botanical species used commercially. 69 Fed. Reg. at 6789.

5. Defendants object to the allegations in paragraph 5 to the extent that Nutraceutical supports the allegations by relying on material outside the administrative record in this case[8] (i.e., Exhibits B and E, attached to Affidavit of C. Hogle in Support of Plaintiffs' Motion for Summary Judgment).

6. Defendants object to the allegations in paragraph 6 because Nutraceutical supports the allegations by relying on material outside the administrative record in this case (i.e., Exhibits B and E, attached to Affidavit of C. Hogle in Support of Plaintiffs' Motion for Summary Judgment).

7. Defendants object to the allegations in paragraph 7 because Nutraceutical supports the allegations by relying on material outside the administrative record in this case (i.e., Exhibits B

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[8] Review in this case is limited to the administrative record. See infra at 23-24.

and E, attached to Affidavit of C. Hogle in Support of Plaintiffs' Motion for Summary Judgment).

8. Defendants object to the allegations in paragraph 8 because Nutraceutical supports the allegations by relying on material outside the administrative record in this case (i.e., Exhibits B and E, attached to Affidavit of C. Hogle in Support of Plaintiffs' Motion for Summary Judgment).

9. Defendants object to the allegations in paragraph 9 because Nutraceutical supports the allegations by relying on material outside the administrative record in this case (i.e., Exhibits B and E, attached to Affidavit of C. Hogle in Support of Plaintiffs' Motion for Summary Judgment).

10. Defendants object to the allegations in paragraph 10 because Nutraceutical supports the allegations by relying on material outside the administrative record in this case (i.e., Exhibits B and E, attached to Affidavit of C. Hogle in Support of Plaintiffs' Motion for Summary Judgment).

15. Defendants object to the allegations in paragraph 15 because they reflect a conclusion of law disputing the statutory interpretation of the term "unreasonable risk" as a risk-benefit analysis.

17. The allegations in the second sentence in paragraph 17 are denied to the extent that they suggest that FDA did not address comments submitted by Nutraceutical during this rulemaking. In the Final Rule, FDA explicitly responded to comments it received that

"expressed the view that low doses of ephedrine alkaloids in dietary supplements do not pose a safety concern and should remain on the market." 69 Fed. Reg. at 6805; see id. at 6828-29 (responding to comments suggesting dose limitations (among other measures) to reduce the risk of adverse events).

18. Defendants object to the allegations in paragraph 18 to the extent that they represent that the effective date of the Final Rule was April 12, 2003. The Final Rule became effective on April 12, 2004. 69 Fed. Reg. at 6788.

19. The allegations in the first sentence in paragraph 19 are denied to the extent that they state FDA did not address the comments submitted by Nutraceutical during this rulemaking. In the Final Rule, FDA explicitly responded to comments it received that "expressed the view that low doses of ephedrine alkaloids in dietary supplements do not pose a safety concern and should remain on the market." 69 Fed. Reg. at 6805. Defendants object to the remaining allegations in paragraph 19 because Nutraceutical supports the allegations by relying on material outside the administrative record in this case (i.e., Exhibit J, attached to Affidavit of C. Hogle in Support of Plaintiffs' Motion for Summary Judgment).

20. Defendants object to the allegations in paragraph 20 because Nutraceutical supports the allegations by relying on material outside the administrative record in this case (i.e., Exhibit J, attached to Affidavit of C. Hogle in Support of Plaintiffs' Motion for Summary Judgment).

21. Defendants object to the allegations in paragraph 21 because Nutraceutical supports the allegations by relying on material outside the administrative record in this case (i.e., Exhibit J, attached to Affidavit of C. Hogle in Support of Plaintiffs' Motion for Summary Judgment). Furthermore, the allegations in paragraph 21 are denied. In the Final Rule, FDA documented that EDS, at a daily dose lower than 10 mg of ephedrine alkaloids, could produce serious adverse health effects, namely cardiovascular risks. 69 Fed. Reg. at 6805; see id. at 6828-29 (responding to comments suggesting dose limitations (among other measures) to reduce the risk of adverse events).

22. Defendants object to the allegations in paragraph 22 to the extent that Nutraceutical supports the allegations by relying on material outside the administrative record in this case (i.e., Exhibit K, attached to Affidavit of C. Hogle in Support of Plaintiffs' Motion for Summary Judgment).

23. Defendants object to the allegations in paragraph 23 to the extent that Nutraceutical supports the allegations by relying on material outside the administrative record in this case (i.e., Exhibit L, attached to Affidavit of C. Hogle in Support of Plaintiffs' Motion for Summary Judgment).

V. ARGUMENT

A. SUMMARY JUDGMENT STANDARD

Summary judgment is appropriate "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no

genuine issue as to any material fact and that the moving party is entitled to judgment as a matter of law." Celotex Corp. v. Catrett, 477 U.S. 317, 322 (1986); see also Anderson v. Liberty Lobby, 477 U.S. 242 (1986); Rakity v. Dillon Cos., 302 F.3d 1152, 1157 (10th Cir. 2002). The movant may demonstrate lack of a genuine issue of material fact either by demonstrating that the non-movant's evidence is not sufficient to establish an essential element of his or her claim, or by submitting affirmative evidence that negates an essential element of the claim. Celotex, 477 U.S. at 322. A fact is material if, "under the governing law, it could have an effect on the outcome of the lawsuit." Rakity, 302 F.3d at 1157. An issue of material fact is genuine only if the non-movant presents facts such that a reasonable jury could find in favor of the non-movant. Planned Parenthood of the Rocky Mountains Services v. Owens, 287 F.3d 910, 916 (10th Cir. 2002) (citation and quotation omitted).

A party may not defeat a motion for summary judgment by simply showing that there is some metaphysical doubt as to the material facts. Matsushita Elec. Indus. Co. v. Zenith Radio, 475 U.S. 574, 586 (1986). Once the movant shows the absence of a genuine issue of material fact, the non-movant cannot merely rest upon his or her pleadings, "but must set forth specific facts showing that there is a genuine issue for trial." Cudjoe v. Independent School Dist. No. 12, 297 F.3d 1058, 1062 (10th Cir. 2002); see also Matsushita Elec. Indus., 475 U.S. at 586.

B. SCOPE OF REVIEW

The scope of the Court's review of the Final Rule is limited to the administrative record. Because Nutraceutical's motion is styled as a motion for summary judgment, Defendants use the

same format in their opposition and cross-motion. Defendants recognize that, in the 10th Circuit, "'Reviews of agency action in the district courts must be processed *as appeals*.'" Southern Utah Wilderness Alliance v. Bureau of Land Management, 147 F. Supp. 2d 1130, 1135-36 (D. Utah 2001) (quoting Olenhouse v. Commodity Credit Corp., 42 F.3d 1560, 1580 (10th Cir. 1994) (emphasis in original)). However, a district court may review agency action on a motion styled by the parties as a motion for summary judgment, so long as the court properly applies review procedures. Id.

Under such review procedures, it is inappropriate for the Court to consider matters outside of the administrative record See Olenhouse, 42 F.3d at 1579-80. Because review is confined to the administrative record, the Court should not consider the exhibits accompanying Nutraceutical's motion that were not before the agency during the rulemaking process, including Exhibits B, E, J, K, and L. Furthermore, Nutraceutical could have submitted Exhibits B, E, and J to FDA for the agency's consideration during the rulemaking process, but did not, and offers no explanation why it failed to do so.

C. THE GOVERNMENT IS ENTITLED TO SUMMARY JUDGMENT BECAUSE FDA HAS MET ITS BURDEN TO SHOW THAT ALL EDS PRESENT AN "UNREASONABLE RISK OF ILLNESS OR INJURY"

Central to this case is whether, in promulgating the Final Rule, FDA has shown that all EDS are adulterated under DSHEA because they present an unreasonable risk of illness or injury when used as labeled or, in the absence of such labeling, under ordinary conditions of use. As explained in detail below, FDA has met its burden. The Final Rule is lawfully promulgated

pursuant to the FDCA and the APA. This Court should reject Nutraceutical's arguments in their entirety and grant summary judgment for the government.[9]

1. FDA'S STATUTORY INTERPRETATION OF UNREASONABLE RISK

a. Standard of review to be applied to FDA's legal interpretation of DSHEA

Under DSHEA, a dietary supplement that presents an "unreasonable risk of illness or injury" is adulterated. 21 U.S.C. § 342(f)(1)(A). FDA's interpretation of "unreasonable risk" to require a balancing of risks and benefits is undoubtedly a permissible construction – indeed, the only plausible construction – of the statute. Thus, FDA's interpretation should be upheld under any standard of review.

FDA believes that Congress unambiguously intended the "unreasonable risk" standard to require a risk-benefit analysis, and that the plain meaning of the statute controls. Nevertheless, even if this Court were to find the phrase "unreasonable risk" ambiguous, the agency's common-sense interpretation of the statutory language should receive deference from the Court. DSHEA's provision requiring the court to decide any issue under 21 U.S.C. § 342(f)(1) on a de

[9] In a related case, in March 2004, NVE, Inc., filed suit to challenge the validity of FDA's Final Rule, claiming that the rule violated DSHEA, the APA, and the due process clause of the Fifth Amendment. On March 31, NVE filed a motion for emergency relief to enjoin enforcement of the Final Rule. The Court denied NVE's motion on April 12, and the Final Rule went into effect that same day. After briefing and oral argument, the Court issued its opinion and related orders regarding the proper standard of review to be applied to the merits of the case. The Court agreed with the government that the Court's review is limited to the administrative record. NVE, Inc. v. Dep't Health and Human Servs. et al., No. 04-999 (D.N.J. Aug. 4, 2004). On November 2, 2004, the United States Court of Appeals for the Third Circuit granted NVE's petition for an interlocutory appeal on this issue.

novo basis governs the court's review of the agency's application of the statutory adulteration standard to the facts, but does not disturb the usual rules of statutory construction.[10]

Under the familiar Chevron framework, "[i]f the intent of Congress is clear, that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." Chevron U.S.A., Inc. v. Natural Resources Defense Council, 467 U.S. 837, 842-43 (1984)("Chevron step 1"). If, however, the statutory language is ambiguous, a court must accord deference to an administrative agency's reasonable interpretation of its own statute. See Chevron, 467 U.S. at 837, 843-44 & n.11 ("Chevron step 2") (in case of ambiguity, court must uphold agency's interpretation if it is permissible under the statute); see also United States v. Mead Corp., 533 U.S. 218, 229 (2001) (where Chevron deference is applicable, "reviewing court has no business rejecting an agency's exercise of its generally conferred authority to resolve a particular statutory ambiguity simply because the agency's chosen resolution seems unwise." (citations omitted)); Pharmanex v. Shalala, 221 F.3d 1151, 1154 (10th Cir. 2000) (affirming FDA's interpretation of "dietary supplement" as that term is used in DSHEA, and, in so doing, according FDA deference "given its special institutional competence regarding the 'facts and circumstances surrounding the subjects regulated,' particularly those which touch and concern competing views of the public interest.") (quoting FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120,132 (2000)). Furthermore, "[r]emedial legislation such

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[10] But see NVE, Inc. v. Dep't Health and Human Servs. et al., No. 04-999, slip op. at 10 (D.N.J. Aug. 4, 2004) (finding that Congress, in DSHEA, "intended all issues, both factual and legal, to be determined de novo," without paying deference to the agency's interpretation), petition for interlocutory appeal on other grounds granted, No. 04-8042 (3d Cir. Nov. 2, 2004).

as the Food, Drug, and Cosmetic Act is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health." United States v. Undetermined Quantities . . . Veterinary Drug, 22 F.3d 235, 238 (10th Cir. 1994).

By mandating that the court decide de novo "any issue under this paragraph," 21 U.S.C. § 342(f)(1), Congress indicated that a de novo standard of review would apply to each of the four ultimate findings of adulteration set forth in the paragraph: a "significant or unreasonable risk of illness or injury" (§ 342(f)(1)(A)), "a new dietary ingredient . . . [lacking] assurance that such ingredient does not present a significant or unreasonable risk of illness or injury" (§ 342(f)(1)(B)), an "imminent hazard to public health or safety" (§ 342(f)(1)(C)), and adulteration caused by a poisonous or deleterious dietary ingredient (§ 342(f)(1)(D)). Nothing in this language refers to Chevron or otherwise suggests that the traditional deference accorded to any agency's construction of statutory language does not apply to the interpretation of the dietary supplement adulteration provisions of DSHEA. The most natural reading of this language evinces not an intent to disavow Chevron but rather to make clear that a de novo standard of review applies to FDA's finding that a dietary supplement is adulterated under any of the four bases set forth in section 342(f)(1).

In United States v. Haggar Apparel Co., 526 U.S. 380, 390 (1999), the Supreme Court found no indication that Congress had meant to dispense with Chevron deference merely because the statute there authorized de novo review of the agency's decision "for all purposes." To the contrary, the Court made clear that "[d]eference to an agency's expertise in construing a statutory

command is not inconsistent with reaching a correct decision," nor is it incompatible with a requirement of de novo review "for all purposes." Id. at 390, 391. Indeed, Haggar suggests that Chevron should be presumed to apply unless Congress explicitly states that it does not.[11]

Interpreting statutes has always been a judicial function, and courts get the last word on what a statute means. When a statute is ambiguous, Chevron and its progeny require deference to permissible agency constructions.[12] Such judicial deference is consistent with de novo judicial review of an agency's construction of a statute. See, e.g., Valansi v. Ashcroft, 278 F.3d 203, 208 (3d Cir. 2002) ("Despite our exercise of de novo review, we will give deference to the agency's interpretation of the [statute] if Congress's intent is unclear."). Indeed, the caselaw is rife with instances in which courts have accorded deference to an agency's construction of ambiguous statutory language while otherwise reviewing the agency's actions de novo.[13] See, e.g., London

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[11] As one commentator has explained, the presumption in favor of Chevron deference is "quite strong." Thomas W. Merrill & Kristin E. Hickman, Chevron's Domain, 89 Geo. L.J. 833, 841 (April 2001). "In effect, the [Haggar] Court seemed to say that Congress must speak explicitly if it wishes to turn off the Chevron doctrine; any doubts and ambiguities, at least as manifested in the statement of the standard of review, will be construed in favor of continued application of Chevron." Id.

[12] The heavy reliance Nutraceutical places on Pactra Indus. v. CPSC, 555 F.2d 677 (9th Cir. 1977), is misplaced. In Pactra Indus., the Ninth Circuit overturned a CPSC regulation because the agency had failed to comply with the procedural requirements of formal rulemaking under the APA, 5 U.S.C. § 556, as required by statute. The court did not address Chevron deference, and because FDA complied with the applicable rulemaking requirements in promulgating the Final Rule, Pactra Indus. lends no support to Nutraceutical's argument that FDA is not entitled to Chevron deference in the instant matter.

[13] Even if Chevron were inapplicable to this case, FDA is, at a minimum, entitled to deference under Skidmore v. Swift & Co., 323 U.S. 134 (1944), under which courts give "considerable and in some cases decisive weight" to statutory interpretations "made in pursuance

v. Polishook, 189 F.3d 196, 199-200 (2d Cir. 1999) (noting "distinction between a court's giving deference to administrative agencies' interpretations and a court's abdicating its duty to make factual determinations"); Wagner Seed Co. v. Bush, 946 F.2d 918, 921 (D.C. Cir. 1991) ("That a private party whose claim has been considered by an administrative agency has a right to trial *de novo* on issues of fact simply does not mean that the court will deny deference to the agency on an issue of statutory interpretation."); cf. Chemical Mfrs. Ass'n v. United States EPA, 859 F.2d 977, 988, 991-92 (D.C. Cir. 1988) (according Chevron deference to agency's interpretation of statute, while conducting "rigorous," "searching," and "demanding" review of factual evidence in record).

b. The meaning of "unreasonable risk"

The term "unreasonable risk" inherently requires a balancing or weighing of factors and virtually commands a comparison of the risks and benefits of a product, i.e., a risk-benefit analysis. Under FDA's view of DSHEA, an "unreasonable risk" exists when a product's benefits do not outweigh its risks in light of the claims and directions for use in the product's labeling or, if the labeling is silent, under ordinary conditions of use.

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of official duty, [and] based upon more specialized experience and broader investigations and information" than a court is likely to have, provided that the administrative decision is carefully and thoughtfully made. Id. at 139-40. Here, FDA's interpretation and implementation of DSHEA involves a "highly detailed" regulatory scheme to which the agency has brought its "specialized experience" to bear. Mead, 533 U.S. at 235. The Final Rule challenged by Nutraceutical "claim[s] the merit of its writer's thoroughness, logic and expertness," and is thus entitled to deference under Skidmore. Id.

The plain meaning of the statute is the starting point of any statutory construction. See, e.g., Resolution Trust Corp. v. Love, 36 F.3d 972, 976 (10th Cir. 1994). DSHEA states that dietary supplements are adulterated if they present a "significant or unreasonable risk of illness or injury."[14] 21 U.S.C. § 342(f)(1)(A). The words "significant" and "unreasonable" have two different meanings. Whereas "significant" involves an evaluation of risk alone, "unreasonable" requires a comparison of risks and benefits. See 69 Fed. Reg. at 6823 ("A risk could be significant but reasonable if the benefits were great enough to outweigh the risks."). Under the plain meaning of the statute, therefore, "unreasonable risk" entails a risk-benefit analysis.

The term "unreasonable risk" is also used in other provisions of the FDCA, e.g., in the provisions related to medical devices. In the medical device classification provisions, Class III devices are distinguished from Class I and Class II devices in part because they present a "potential unreasonable risk of injury or illness." See 21 U.S.C. § 360c(a)(1). The legislative history of the device provisions provides an indication of how Congress intended FDA to interpret the term "unreasonable risk" in this context. The House Committee Report states: "the requirement that a risk be unreasonable contemplates a balancing of the possibility that illness or injury will occur against the benefits of use." H. Rep. 853, 94th Cong., 2d Sess. 19 (1976). Thus, FDA's construction of "unreasonable risk" with respect to dietary supplements is consistent with the way Congress has defined that term in other parts of the same statute.

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[14] Because FDA concluded that EDS pose an unreasonable risk, it was not necessary for the agency to address DSHEA's significant risk standard.

Additionally, FDA's interpretation of "unreasonable risk" is consistent with interpretations of similar statutory provisions outside of the FDCA. For example, the Toxic Substances Control Act contains an "unreasonable risk" standard, see 15 U.S.C. § 2605(a), and the legislative history indicates that Congress intended this standard to be evaluated using a balancing test. See H. Rep. 94-1341, 94th Cong., 2d Sess. 32 (1976).

In the Final Rule, FDA concluded that, based on the plain meaning of the statutory language, as well as legislative history, "Congress unambiguously intended that an assessment of 'unreasonable risk' in the dietary supplement context [i.e., in 21 U.S.C. § 342(f)(1)(A)] should entail a risk-benefit analysis." 69 Fed. Reg. at 6823.

2. FDA'S SHOWING OF UNREASONABLE RISK

FDA concluded that EDS are adulterated under 21 U.S.C. § 342(f)(1)(A) because their minimal benefits weighed against their substantial risks presented an unreasonable risk of illness or injury under the labeled conditions of use or, in the absence of such labeling, under ordinary conditions of use. See 69 Fed. Reg. at 6788. In reaching this conclusion, FDA evaluated the seriousness of the risks and the quality and persuasiveness of the totality of the evidence supporting the presence of those risks. Id. at 6799. FDA then weighed the risks against the benefits, taking into account the quality and persuasiveness of the evidence supporting the existence of those benefits and the importance of those benefits. Id. FDA gave more weight to benefits that improve health outcomes, especially in the long term, than to benefits that are temporary or rely on subjective measures such as feeling better or improved appearance. Id. In

particular, FDA stated that it would consider a sustained, long-term weight loss in an overweight person to be a much more important benefit than short-term weight loss because long-term weight loss in overweight individuals reduces the risk of morbidity and mortality (e.g., heart attacks and strokes), whereas short-term weight loss does not. Id.

FDA's decision to ban all EDS because they present an unreasonable risk of illness or injury was based on a careful, objective analysis of the most current information. The agency compiled and evaluated the relevant scientific data and literature regarding the pharmacology of products containing ephedrine alkaloids, clinical studies, published case reports, and adverse event reports; commissioned expert reviews of the scientific evidence; and assessed the findings of the expert reviews. 69 Fed Reg. at 6788, 6798, 6800-11, 6814-22. Furthermore, FDA reviewed each of the thousands of comments submitted to the agency during the rulemaking process (including those submitted by Nutraceutical). Id. at 6792-93. After a comprehensive evaluation of the data, FDA found that, based on the best available scientific data, EDS do not provide a health benefit sufficient to outweigh the risks of stroke, heart attack, worsened congestive heart failure, cardiac arrhythmia, and death. Id. at 6788-89, 6793, 6798, 6825-27. Therefore, FDA concluded that all such products, when used as labeled or, in the absence of such labeling, under ordinary conditions of use, present an unreasonable risk of illness or injury. Id.

FDA found that multiple studies demonstrate that EDS raise blood pressure and increase heart rate. 69 Fed. Reg. at 6827. As a result, EDS expose users to several risks, including stroke and heart attack that can result in death, and increased morbidity and mortality from worsened

heart failure and pro-arrhythmic effects. Id. FDA's evaluation determined that, although the *pro-arrhythmic effects of these products typically occur only in susceptible individuals*, the long-term risks from elevated blood pressure can occur even in non-susceptible, healthy individuals. Id. FDA concluded that these risks are not outweighed by any known or reasonably likely benefits either when EDS are used for their labeled indications, such as weight loss, athletic performance, eased breathing, and increased energy or alertness, or under ordinary conditions of use. Id.

FDA determined that the best scientific evidence of benefit is for modest short-term weight loss; however, FDA concluded that such benefit is not sufficient to bring about an improvement in health that outweighs the concomitant health risks. 69 Fed. Reg. at 6827. FDA also found that the other possible benefits, such as increased energy, eased breathing, and enhancement of athletic performance, have less scientific support, and that, even assuming that these possible benefits in fact occur, they are also insufficient to outweigh identified health risks that can lead to serious long-term or permanent consequences like heart attack, stroke, and death. Id. at 6825-27.

FDA concluded that the published controlled studies of the use of ephedrine alkaloid products for weight loss cited in comments submitted to the agency during rulemaking cannot establish the safety profile of EDS. 69 Fed. Reg. at 6803-04; see also id. at 6802, 6808 and Refs. 50-52. In reaching this conclusion, FDA relied on several factors. First, many of the most serious risks, such as strokes or heart attacks (resulting from elevated blood pressure),

arrhythmias, or worsened heart failure, are relatively infrequent or are delayed and, therefore, will not be detected in studies using small populations as these studies did. Id. at 6803-04. Second, these studies often had other important design limitations, such as lack of adequate controls, including the absence of placebo control groups in some studies. Id. In addition, persons with known cardiovascular disease or cardiovascular risks were usually excluded and, thus, these studies were not designed to detect serious adverse effects in susceptible individuals. Id. Furthermore, these studies were not adequately designed to measure blood pressure changes and thus provide no data to measure adverse effects. Id. FDA concluded that, given these limitations, it is not surprising that the studies do not report serious adverse events.[15] Id.

FDA also determined that the risks associated with EDS cannot be adequately mitigated through other regulatory measures available to the agency for dietary supplements, such as warnings in labeling or dose limitations. 69 Fed. Reg. at 6806, 6829. Because warning labels are beneficial only when people are able to identify the risk about which they are being warned, the fact that individuals may be unaware of their susceptibility is an important reason why warning labels on EDS are insufficient to make the risks of EDS reasonable. Id. at 6805-06.

FDA determined that people with high blood pressure, coronary artery disease, and congestive heart failure are at greater risk of experiencing adverse health effects of EDS. 69 Fed. Reg. at 6802. FDA also found that, although approximately one in four adults has high blood

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[15] FDA's evaluation included a review of the 56 articles cited by RAND as meeting the criteria for RAND's efficacy analysis and a subset of 460 references cited by RAND as being rejected from that analysis. See 69 Fed. Reg. at Ref. 81.

pressure, 31 percent of this group are unaware of their condition. Id. Many individuals are also unaware that they have coronary artery disease or early heart failure because these conditions may not initially cause prominent symptoms. Id. Overweight and obese individuals are particularly prone to hypertension, coronary artery disease, and/or congestive heart failure. Id. In sum, the very individuals who use the products for weight loss are the most at risk.

FDA concluded that dose limitations cannot change the unfavorable risk-benefit ratio of these products and that all EDS, regardless of the recommended dosage, present an unreasonable risk of illness or injury. 69 Fed. Reg. at 6829. After the 1997 proposed rule was published, FDA commissioned a scientific review to evaluate whether low doses of ephedrine alkaloids in EDS present a risk of adverse events. Id. at 6805 and Refs. 84, 85. The review determined that even "'a dose of 1.5 mg every 4 hours (a daily dose of 9 mg) would produce cardiovascular effects *that may be dangerous alone, or in association with risk factors.*'" Id. at 6805 (quoting Ref. 84 at p. 6). Furthermore, this scientific review concluded that a "safe dose" of ephedrine alkaloids in dietary supplements cannot be identified.[16] Id. at 6805 and Ref. 84. Based on this assessment, together with the well-known pharmacology of ephedrine alkaloids (supra at 13-14), the available scientific studies (supra at 14-18), AERs (supra at 18-19), expert reviews (supra at 18-

[16] FDA also noted that, in the 1996 Food Advisory Committee meeting, several committee members stated that, based on the available data, no safe level of ephedrine alkaloids could be identified for use in dietary supplements. 69 Fed. Reg. at 6805 and Ref. 86. Consequently, they recommended removing EDS from the market. Id. and Ref. 87.

19, 35), and other materials in the administrative record, FDA concluded that an unreasonable risk of illness or injury is presented by all EDS.[17] Id. at 6796.

The foregoing evidence in the administrative record demonstrates that all EDS, including the dosages sold by Nutraceutical, present an unreasonable risk of illness or injury.[18] Therefore, the Final Rule is a proper exercise of the agency's authority and is not arbitrary, capricious, or otherwise unlawful under the APA.

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[17] The CANTOX Health Sciences International (CANTOX) review attempted to establish a level of ephedrine alkaloids at which there were no adverse effects. 69 Fed. Reg. at 6805. The CANTOX review, sponsored by an industry trade group, was a quantitative risk assessment that used Institute of Medicine (IOM) methods to determine a safe upper level (called the No Observed Adverse Effect Level (NOAEL)) for botanical ephedrine alkaloids used in dietary supplements. Id. at 6808. FDA concluded that this review cannot be used to establish a NOAEL for ephedrine alkaloids used in dietary supplements because the review: (1) used an inappropriate risk assessment model; (2) deviated from the criteria and procedures established by the IOM; and (3) used data with underlying deficiencies. Id. at 6808-09.

[18] Without citing any authority, Nutraceutical contends that "FDA needs a preponderance of the science-based evidence to meet its burden [of proof]" in support of the Final Rule. Pl. Br. at 7. Although Nutraceutical admits that proof of an actual injury to the public is not necessary to sustain the Final Rule, it argues that the evidence cited in the Final Rule is insufficient to satisfy FDA's burden of proof. Id. at 7-8. Nutraceutical, however, does not claim that FDA improperly relied on incompetent evidence in promulgating the Final Rule. Nor does it claim that FDA improperly weighed the evidence in the administrative record. Instead, Nutraceutical merely cites, inappropriately, to materials outside the administrative record (to support its contention that not all doses of EDS pose an unreasonable risk of illness or injury), and makes conclusory legal arguments regarding FDA's burden of proof, without explaining why or in what sense FDA failed to satisfy its burden. Therefore, and because, as shown above, FDA did in fact satisfy its burden of demonstrating that EDS present an unreasonable risk of illness or injury, Nutraceutical's claim is baseless.

D. NUTRACEUTICAL'S ARGUMENTS ARE BASELESS AND ITS MOTION FOR SUMMARY JUDGMENT SHOULD BE DENIED

As a preliminary matter, nearly every argument contained in Nutraceutical's brief is peppered with citations to the 1994 Senate Committee Report 103-410. See Pl. Br. at 4, 5, 6, 7, 10, 12, 16, 17, 20. Because there is no ambiguity in the language of 21 U.S.C. § 342(f)(1)(A), this Court should not resort to analysis of legislative history.[19] See United States v. Gonzales, 520 U.S. 1, 6 (1997) ("Given the straightforward statutory command, there is no reason to resort to legislative history."); Ratzlaf v. United States, 510 U.S. 135, 147-48 (1994) (rejecting attempt to "resort to legislative history to cloud a statutory text that is clear"); Connecticut Nat'l Bank v. Germain, 503 U.S. 249, 253-54 (1992).

Even if resort to legislative history were proper, Nutraceutical's reliance on the Senate Committee Report does not advance its case. In several instances, the language quoted by Nutraceutical does not refer to the "unreasonable risk" provision at issue in this case, i.e., 21 U.S.C. § 342(f)(1)(A), but to one of the other bases of adulteration codified at 21 U.S.C. § 342(f)(1). See, e.g., Pl. Br. at 5, 6, 16 (quoting language on page 36 of the Committee Report

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[19] *Members of Congress took the unusual step of explicitly disclaiming the Senate* Committee Report as part of DSHEA's legislative history. The sponsors of the legislation drafted a "Statement of Agreement" and declared that the statement "comprises the entire legislative history for [DSHEA]." 140 Cong. Rec. S14801 (Oct. 7, 1994), reprinted in 1994 U.S.C.C.A.N. 3523. To eliminate any room for doubt, the statement provides that "[i]t is the intent of the chief sponsors of the bill . . . that no other reports or statements be considered as legislative history for the bill." Id. It is not necessary for this Court to resolve the question of the effectiveness of this disclaimer because the language of the statutory provision at issue in this case is unambiguous.

that reflects the adulteration standard codified at 21 U.S.C. § 342(f)(1)(D)).[20] In other instances, Nutraceutical offers a portion of the Committee Report for a proposition that it does not support. Compare Pl. Br. at 10, 12, 17 (asserting that dietary supplements and foods must be regulated precisely in the same manner) with S. Rep. 103-410 at 22 (setting forth specific situations, applicable only to dietary supplements, in which a dietary supplement would be deemed adulterated under the Senate version of the bill).

1. DSHEA REQUIRES AN ASSESSMENT OF BENEFIT AS PART OF ITS UNREASONABLE RISK STANDARD

Nutraceutical presents a variety of assertions in support of its claim that "unreasonable risk" does not require a weighing of benefits against risks. All of these assertions are inaccurate and unsupportable.

Nutraceutical argues that, because the FDCA "does not require proof of benefit before a food or dietary supplement is legally saleable," Pl. Br. at 9, the Final Rule's risk-benefit analysis is contrary to the FDCA.[21] See Pl. Br. at 9-11. DSHEA provides that a dietary supplement is

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[20] The Committee Report cites as "(f)(3)" the version of what ultimately became "(f)(1)(D)" because the Committee Report focuses on the Senate version of S. 784. However, the House version of the bill was substituted, as an amendment, before final approval by the Senate. 140 Cong. Rec. S14798-01, 14801 (Oct. 7, 1994). The House amendment contained several substantive modifications to the Senate version regarding the adulteration standards codified at 21 U.S.C. § 342(f)(1).

[21] Nutraceutical claims that the FDCA's treatment of dietary ingredients demonstrates the inappropriateness of FDA's new "proof of benefit" requirement because Congress "recognized as not adulterated, i.e., as lawfully saleable, every dietary supplement ingredient marketed in the United States before the effective date of the DSHEA, i.e., before October 14, 1994." Pl. Br. at 10. In fact, the FDCA provisions cited by Nutraceutical exclude dietary ingredients that were marketed before October 14, 1994, from the definition of a "new dietary ingredient," 21 U.S.C.

adulterated if it "presents an . . . unreasonable risk of illness or injury" under the labeled conditions of use or, if the labeling is silent, under ordinary conditions of use. 21 U.S.C. § 342(f)(1)(A). FDA conducted a risk-benefit analysis, found that the claimed benefits of EDS (weight loss, improved athletic performance, eased breathing, increased alertness) were minimal, that the risks (stroke, heart attack, death) were substantial and life-threatening, and, on that basis, concluded that EDS present an unreasonable risk of illness or injury. The Final Rule applies only to EDS and does not create a new requirement that evidence of a benefit must be demonstrated by any and all dietary supplements before they can legally be marketed. Nutraceutical offers no explanation for why it contends that the Final Rule creates such a requirement.[22]

Nutraceutical claims that FDA erred by weighing the benefits of EDS against the risks because unreasonable risk is "appropriately evaluated without any examination of benefit." Pl. Br. at 12. Nutraceutical argues that because the word "benefit" does not appear in section 342(f)(1)(A), unreasonable risk must mean that "a low level of risk (one that does not cause

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§ 350b(c). Therefore the adulteration provisions governing new dietary ingredients, 21 U.S.C. § 342(f)(1), and the corresponding prohibited act, 21 U.S.C. § 331(v), do not apply to such dietary ingredients. The provisions do not deem these dietary ingredients "not adulterated," as Nutraceutical contends, but rather, the cited provisions are merely inapplicable to dietary ingredients marketed prior to October 1994.

[22] Nutraceutical argues that, because food safety determinations "do not include a weighing of a food's benefit," FDA's risk-benefit analysis in the Final Rule is contradictory to the FDCA. See Pl. Br. at 11. Even assuming that statement were true, Nutraceutical's position lacks merit. Foods and dietary supplements are regulated differently under the FDCA. See infra at 46-47.

significant illness or injury) is reasonable, and a high level of risk (one that does cause such illness or injury) is unreasonable." Id. Nutraceutical fails to cite any support for this tunnel-vision definition of "unreasonable risk."

Nutraceutical's interpretation of DSHEA would render the term "unreasonable" superfluous. The statutory provision states that dietary supplements are adulterated if they present a "significant or unreasonable risk of illness or injury." 21 U.S.C. § 342(f)(1)(emphasis added). As explained above, see supra at 31, "significant" involves an evaluation of risk alone, whereas "unreasonable" requires a comparison of risks and benefits. 69 Fed. Reg. at 6823. Because the definition of "unreasonable risk" put forth by Nutraceutical would eclipse the meaning of "significant" risk, such statutory construction is impermissible. See Duncan v. Walker, 533 U.S. 167, 174 (2001); United States v. Tsosie, 376 F.3d 1210, 1217 (10th Cir. 2004) (courts are guided by the "traditional canon of statutory construction that courts should avoid statutory interpretations which render provisions superfluous").

As explained above, "unreasonable risk" has been similarly defined elsewhere in the FDCA, namely in the provisions related to medical devices, as well as in other federal statutes. 69 Fed. Reg. at 6823. Nutraceutical claims that FDA's citation to the medical device classification provisions, 21 U.S.C. § 360c(a)(1), to support the Final Rule's definition of "unreasonable risk" is "misplaced" because a different medical device provision, 21 U.S.C. § 360c(a)(2), which governs the determination of the safety and effectiveness of a device, explicitly provides for a weighing of the probable benefit against the probable risk. Pl. Br. at 12-

13. The provision Nutraceutical cites in its brief, however, does not contain the term "unreasonable risk." The medical device legislative history cited by FDA in the Final Rule, on the other hand, speaks directly to Congress' intended meaning of "unreasonable risk" in the FDCA. See supra at 31-32. Nutraceutical's argument is thus unavailing.

According to Nutraceutical, "FDA's risk/benefit test demands that a supplement produce a significant benefit to offset even the slightest evidence of risk." Pl. Br. at 9; see also id. at 11. Nutraceutical is wrong. FDA's risk-benefit calculus involves not only an examination of the seriousness of the risks and the evidence to support the presence of those risks, but also the importance of the benefits and the evidence to support the existence of those benefits. 69 Fed. Reg. at 6799.

As supported by ample evidence in the Final Rule, the adverse health effects associated with EDS – heart attack, stroke, and death – are undeniably serious. Id. at 6825. When FDA noted in the preamble to the Final Rule that, "[i]n the absence of a sufficient benefit, the presence of even a relatively small risk of an important adverse health effect to a user may be unreasonable," id. at 6788 (emphasis added), the "small risk" that the agency was referring to was not to a risk of a minor adverse event, but instead to the frequency of occurrence or likelihood of an important health risk.

Nowhere in the Final Rule does FDA state that a "significant" benefit must be demonstrated to outweigh even a slight risk associated with a dietary supplement. In fact, the Final Rule explicitly states that "risks that are insignificant and reasonable in light of the benefits

from the supplement [as labeled or, if the labeling is silent, under ordinary conditions of use] would not render a dietary supplement adulterated." 69 Fed. Reg. at 6825. In short, FDA did not create a minimum threshold that any and all benefits of EDS must exceed. Instead, pursuant to the language of DSHEA, all of the known and reasonably likely benefits of EDS were weighed against the known and reasonably likely risks of such products. See, e.g., 69 Fed. Reg. at 6798-99, 6818-22, 6825-27. The risks simply outweighed the benefits.

Nutraceutical's challenge to FDA's risk-benefit analysis in the Final Rule lacks merit and therefore should be rejected by this Court.

2. EVIDENCE IN THE ADMINISTRATIVE RECORD ESTABLISHES THAT EDS WITH 10 MG OR LESS OF EPHEDRINE ALKALOIDS PER DAILY DOSE PRESENT AN UNREASONABLE RISK OF ILLNESS OR INJURY

Nutraceutical claims that the administrative record in support of the Final Rule lacks adequate scientific evidence to establish that EDS containing 10 mg or less of ephedrine alkaloids per daily dose present an unreasonable risk of illness or injury. See Pl. Br. at viii. Nutraceutical contends that FDA relied solely on health risks posed by EDS with "high levels of ephedrine alkaloids" in its decision to ban all EDS, including products with low daily doses of ephedrine alkaloids. Id. at 13. According to Nutraceutical, the agency "utterly failed to satisfy the burden for dietary supplements containing 10 mg of ephedrine alkaloids or less per daily dose," id. at 14, and therefore, its product cannot be deemed adulterated pursuant to the Final Rule. Id. at 2.

Nutraceutical's arguments suffer from three critical errors. First, the actual potency of Nutraceutical's product is undetermined. Any allegation in Nutraceutical's motion that its product contains a specific amount of ephedrine alkaloids is belied by its admission that it has "assumed a potency" for purposes of its motion and that "actual content may vary based on harvest season and other factors." See Pl. Br. at viii n.6. Moreover, the directions for use on Nutraceutical's product label have varied over time. For instance, one label directed users to "[t]ake as a food supplement two to eight capsules daily," potentially yielding a daily dosage up to four times greater than 10 mg per day. See A.R. 72970, attached at Exhibit II (along with A.R. 72967-969, 72971-976 to provide context).

Second, Nutraceutical appears to equate a lack of clinical trial evidence with an absence of any evidence.[23] See, e.g., Pl. Br. at 7 ("FDA found no clinical trial evidence . . . .") and 8 (implying that the agency does not possess "clinical trial proof" of unreasonable risk of EDS at low dose levels). However, clinical trial experience is not the only valid, reliable scientific evidence that can support FDA's decision to declare EDS adulterated. Clinical trials are not always available; nor is such evidence always feasible to obtain. Although Congress placed the ultimate burden on the government to show "unreasonable risk," once such risk is identified, Congress did not intend to tie FDA's hands until double-blind, placebo-controlled, clinical studies are conducted or to preclude FDA from taking action if such clinical studies cannot be

[23] Defendants presume that the term "clinical trial evidence" as used by Nutraceutical is intended to refer to double-blind, placebo-controlled, clinical studies.

conducted.[24] FDA relied on the best available science to conclude that all EDS present an unreasonable risk of illness or injury, regardless of how they are formulated or labeled, because the substantial risks outweigh the minimal benefits that may result from use of the products. See, e.g., 69 Fed. Reg. at 6796.

Third, FDA's decision to ban all EDS was not based solely on scientific evidence regarding higher-dose EDS.[25] In addition to all of the evidence detailing the serious health risks associated with EDS generally, FDA commissioned a scientific review specifically to address the issue of low-dose products. In fact, FDA documented that EDS, at a daily dose lower than 10 mg of ephedrine alkaloids "'would produce cardiovascular effects that may be dangerous alone, or in association with risk factors.'" 69 Fed. Reg. at 6805 (quoting Ref. 84 at p. 6). These health risks are the same cardiovascular risks associated with higher-dose EDS. See id. and Ref. 84. Regardless of dose, the minimal benefits of EDS are outweighed by the substantial risks

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[24] Ethical considerations may prevent certain clinical trials from being conducted to evaluate the adverse effects of EDS, e.g., the arrhythmogenic potential of ephedrine alkaloids in patients with coronary artery disease, the adverse effects of ephedrine alkaloids in people with heart failure, or the consequences of raising blood pressure in various populations. 69 Fed. Reg. at 6798, 6799.

[25] In making this argument, the government does not concede that, in order to ban EDS, it must prove that EDS present a significant or unreasonable risk of illness or injury "at every dose level." See Pl. Br. at 6. Rather, the agency need only determine, as it did in this case, that a safe dose of ephedrine alkaloids in EDS cannot be identified. See supra at 36-37. Were Nutraceutical correct, the agency would effectively be prevented from ever banning a dietary supplement. As a practical matter, scientific studies do not, and indeed cannot, evaluate a product's risks at every potential dose level. Under Nutraceutical's view, dietary supplement manufacturers could alter, on an incremental, cat and mouse basis, the recommended dosages of their products in continuous attempts to evade adverse findings in the scientific literature. This illogical result invalidates Nutraceutical's position.

associated with the use of these products. The agency found that low doses of ephedrine alkaloids in dietary supplements present an unreasonable risk and should not remain on the market. See id. at 6805; see also id. at 6829.

The risks attributed to EDS are due to their inherent pharmacological and physiological effects. 69 Fed. Reg. at 6829. Nutraceutical's product is not pharmacologically unique and poses the same risks of serious adverse health effects as other EDS. No restriction, short of a ban, can make Nutraceutical's product, or any other EDS, safe. See id. (concluding that dose limitations cannot change the unfavorable risk-benefit ratio of these products); see also id. at 6806 (discussing the ineffectiveness of warning labels on EDS). FDA has demonstrated that all EDS, including dietary supplements containing daily dosages of ephedrine alkaloids alleged present in Nutraceutical's product, pose an unreasonable risk of illness or injury and are thereby adulterated under DSHEA.

3. FDA'S TREATMENT OF FOODS AND DIETARY SUPPLEMENTS IS NOT INCONGRUOUS

Nutraceutical takes issue with the Final Rule because it does not apply to conventional food products that contain ephedrine alkaloids. According to Nutraceutical, such distinction reflects "disparate treatment of ephedrine alkaloids in conventional foods and dietary supplements." Pl. Br. at 17. However, Nutraceutical fails to recognize that the Final Rule could not apply to conventional foods. The Final Rule is based on an adulteration provision, 21 U.S.C. § 342(f)(1), that applies only to dietary supplements and dietary ingredients in dietary supplements. By definition, dietary supplements are products that are not represented for use as

conventional foods. See 21 U.S.C. § 321(ff)(2)(B) (defining "dietary supplement" in part as a product that "is not represented for use as a conventional food or as a sole item of a meal or the diet"). Therefore, the statute permits, and indeed requires, dietary supplements to be treated differently from conventional foods for various purposes, including an adulteration finding within the meaning of 21 U.S.C. § 342(f)(1). Thus, far from being "at odds with its own governing statute," Pl. Br. at 17, FDA's actions are squarely within the mandate of the FDCA.

In addition, although the dietary supplement adulteration provision does not apply to conventional foods, it does not follow that conventional foods containing ephedrine alkaloids are lawful under the FDCA. Cf. Pl. Br. at 17, 20. Substances intentionally added to a conventional food that contains other ingredients are food additives under 21 U.S.C. § 321(s), unless they are generally recognized as safe (GRAS) or fall under another exception to the food additive definition. Because ephedrine alkaloid-containing botanicals are not GRAS, they would generally be considered unsafe food additives when used in a conventional food. See 21 U.S.C. § 348(a). A food that contains an unsafe food additive is adulterated under 21 U.S.C. § 342(a)(2)(C) and cannot be legally marketed under the FDCA.

To the extent that FDA regulates dietary supplements and conventional foods differently, these differences are required by the differences in the statutory provisions that apply to these two categories of products. Where, as here, Congress expressly provided that dietary supplements be subject to the "unreasonable risk" standard that does not apply to conventional foods, FDA may implement that provision without violating the APA.

4. NUTRACEUTICAL RECEIVED ADEQUATE NOTICE OF THE FINAL RULE

Nutraceutical claims that "FDA violated the APA, 5 U.S.C. § 553, when it failed to give notice of its intent to create a new test for evaluating dietary supplement adulteration." Pl. Br. at 21. FDA in fact provided the public, and Nutraceutical in particular (as evidenced by Nutraceutical filing several comments), with adequate notice of the Final Rule, including FDA's reliance on 21 U.S.C. § 342(f)(1)(A) as authority for regulating EDS. Further, FDA's interpretation of the "unreasonable risk" standard set forth at 21 U.S.C. § 342(f)(1)(A) does not constitute a separate substantive rule requiring separate notice and comment under the APA. Nutraceutical's claim that it did not receive adequate notice or that FDA failed to follow applicable legal requirements is hence without merit.

The APA requires agencies to provide notice of proposed rules in the Federal Register. 5 U.S.C. § 553(b). The notice must include, among other things, "either the terms or substance of the proposed rule or a description of the subjects and issues involved." 5 U.S.C. § 553(b)(3); 21 C.F.R. § 10.40(b)(viii). After providing notice, the agency must "give interested persons an opportunity to participate in the rulemaking through submission of written data, views, or arguments," and must consider the comments received. 5 U.S.C. § 553(c).

Notice is adequate under the APA if it facilitates "meaningful" participation by the public by "fairly appris[ing] interested persons" of the issues in the rulemaking. United Steelworkers v. Marshall, 647 F.2d 1189, 1221 (D.C. Cir. 1980) (quoting American Iron & Steel Inst. v. United States EPA, 568 F.2d 284, 293 (3d Cir. 1977)). However, "the notice need not

specifically identify 'every precise proposal which [the agency] may ultimately adopt as a Final Rule.'" Chemical Mfrs. Ass'n v. United States EPA, 870 F.2d 177, 203 (5th Cir. 1989) (quoting United Steelworkers of America v. Schuylkill Metals, 828 F.2d 314, 317 (5th Cir. 1987) (internal citations omitted)).

Agencies "undoubtedly have authority to promulgate a Final Rule that differs in some particulars from its proposed rule [because] . . . '[a] contrary rule would lead to the absurdity that . . . the agency can learn from the comments on its proposals only at the peril of starting a new procedural round of commentary.'" See Small Refiner Lead Phase-Down Task Force v. United States EPA, 705 F.2d 506, 546-47 (D.C. Cir. 1983) (quoting International Harvester Co. v. Ruckelshaus, 478 F.2d 615, 632 n. 51 (D.C. Cir. 1973)). In determining the adequacy of notice, the Court must strike a balance between the agency's need to change the Final Rule based on comments, new information, or further consideration of the issue, and the public's right to participate meaningfully in the promulgation of the Final Rule. See Small Refiner, 705 F.2d at 546-547. In striking this balance, courts apply the "logical outgrowth" test. See South Terminal Corp. v. EPA, 504 F.2d 646 (1st Cir. 1974).

"Logical outgrowth" describes the extent to which a Final Rule may vary from a proposed rule without violating the APA's notice-and-comment requirements. "The question is typically whether the agency's Final Rule so departs from its proposed rule as to constitute more surprise than notice." Air Transp. Ass'n of Am. v. FAA, 169 F.3d 1, 7 (D.C. Cir. 1999)

(emphasis added). Put another way, the test is whether the regulated party "should have anticipated that such a requirement might be imposed." Small Refiner, 705 F.2d at 549.

In this case, the 1997 proposed rule and subsequent notices provided ample notice of the Final Rule. The substantive issue involved in both the proposed and Final Rule is the same, namely whether safety concerns associated with EDS warrant restrictions on marketing. Compare 62 Fed. Reg. at 30697-30703 (Proposed Rule) with 69 Fed. Reg. at 6798-6807 (Final Rule). From 1997 until the Final Rule[26] was promulgated, FDA gave notice that it was considering the issues involved in the potential health risks of EDS, and, in March 2003, FDA specifically stated that it was seeking comments on whether EDS presented an "unreasonable risk of illness or injury." See 68 Fed. Reg. 10417, 10419-20. The major difference between the proposed and Final Rule, as well as the notices issued after the proposed rule but before the Final Rule, is the extent of the regulatory restrictions. FDA's decision to declare all EDS adulterated because they present an unreasonable risk of illness or injury is fairly foreshadowed in the proposed rule, subsequent notices, and comments advanced during the rulemaking.

Nutraceutical cannot now complain that it received inadequate notice about the Final Rule or, in particular, FDA's decision to declare EDS adulterated based on the unreasonable risk standard. In fact, Nutraceutical submitted several comments to FDA in response to Federal Register notices before the Final Rule was promulgated, contending each time that, in essence, its product did not pose an unreasonable risk. Further, in discussing the meaning of "significant

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[26] Like the Final Rule, the proposed rule relied on section 342(f)(1)(A) as FDA's authority for regulating EDS. See, e.g., 62 Fed. Reg. at 30693, 30695.

or unreasonable risk" in its comments, Nutraceutical acknowledged that FDA would be defining and applying this standard in promulgating any regulation under DSHEA governing EDS. See A.R. 99722 (Letter from Nutraceutical Corp. to Dockets Management Branch, FDA (April 7, 2003)), attached at Exhibit III. These comments belie any notion that Nutraceutical was surprised by anything in the Final Rule. See Shell Oil Co. v. United States EPA, 950 F.2d 741, 757 (D.C. Cir. 1991) (noting that comments on the issue are evidence that the public received adequate notice).

Nutraceutical's claim that FDA's interpretation of "unreasonable risk" somehow required a separate notice and comment procedure similarly lacks merit. The risk-benefit analysis contained in the Final Rule simply is FDA's interpretation of the "unreasonable risk" standard of DSHEA, 21 U.S.C. § 342(f)(1)(A). The mere fact that FDA interpreted the "unreasonable risk" prong of DSHEA to require a balancing of the known and reasonably likely risks against the known and reasonably likely benefits of EDS did not create the need for a separate rulemaking.[27] Contrary to Nutraceutical's assertions, the specific risk-benefit analysis contained in the Final Rule is not a substantive rule. The authority upon which Nutraceutical relies, see Pl. Br. at 22, states that a substantive rule "establishes a standard of conduct which has the force of law." American Mining Congress v. Marshall, 671 F.2d 1251, 1263 (10th Cir. 1982) (quoting Pacific Gas & Elec. Co. v. Fed. Power Comm'n, 506 F.2d 33, 38 (D.C. Cir. 1974)). The only

[27] Indeed, the opposite conclusion would render administrative rulemaking virtually impossible, as agencies would be required to undertake multiple notice and comment procedures *every time they attempted to apply a statute – one for the manner in which the agency interprets a* statutory or regulatory provision, and one for the substantive result of that interpretation.

"substantive rule" at issue here is the Final Rule, which concluded that EDS are adulterated and, therefore, can no longer be marketed. This finding establishes a "standard of conduct" relating to EDS, has the force of law, and was subject to the notice and comment requirements, with which FDA complied.

Nutraceutical also contends that the risk-benefit analysis in the Final Rule creates a standard of conduct because "[i]n future adulteration cases before FDA involving other dietary supplements and ingredients, the risks and benefits of various products will be assessed under the newly established risk/benefit test." Pl. Br. at 22.[28] In fact, it is the language of DSHEA itself, i.e., "unreasonable risk," that requires such a risk-benefit analysis. FDA did not create or adopt a new standard for determining when a dietary supplement is adulterated; Congress created the standard when it enacted DSHEA. FDA did, in the Final Rule, explain for the first time its interpretation of "unreasonable risk" as used in 21 U.S.C. § 342(f)(1)(A), 69 Fed. Reg. at 6794, but that does not equate to the creation of a new standard of conduct. See Reno-Sparks Indian Colony v. United States EPA, 336 F.3d 899, 909-910 (9th Cir. 2003) (explanation of agency's interpretation of pre-existing statute did not constitute substantive rule requiring notice and comment); General Motors Corp. v. Ruckelshaus, 742 F.2d 1561, 1565 (D.C. Cir. 1984)

[28] In support of this argument, Nutraceutical cites, in part, to material outside of the administrative record, which is inappropriate as review in this case is limited to the record. See supra at 23-24.

(same).[29] Nutraceutical's claims that FDA violated the notice and comment provisions of the APA should be rejected by this Court.

E. THE FINAL RULE IS NOT A TAKING UNDER THE FIFTH AMENDMENT TO THE U.S. CONSTITUTION

As shown above, the Final Rule meets the requirements of DSHEA and the APA. In its complaint, Nutraceutical alleges that, even if the Final Rule is a valid exercise of FDA's authority, the Rule constitutes a taking under the Fifth Amendment, pursuant to which Nutraceutical is due just compensation. See Cmplt. ¶¶ 47-54, 55(f). Nutraceutical is wrong. First, this Court does not have jurisdiction to entertain Nutraceutical's takings claim, as such a claim must be brought in the United States Court of Federal Claims. Second, even if this Court does have jurisdiction, the Final Rule does not constitute a taking.

1. THIS COURT LACKS JURISDICTION TO ENTERTAIN NUTRACEUTICAL'S TAKINGS CLAIM

Nutraceutical must bring any takings claim in the United States Court of Federal Claims, and not in this Court. The Tucker Act, 28 U.S.C. § 1491, vests the Court of Federal Claims with exclusive jurisdiction to entertain any claim against the federal government to recover damages pursuant to the Constitution, a statute, a regulation, or a contract with the United States, whenever that claim exceeds $10,000. See Presault v. Interstate Commerce Comm'n, 494 U.S.

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[29] In any event, as discussed supra at 31-32, the plain meaning of "unreasonable risk" requires a risk-benefit analysis. For this reason also, any alleged failure to disclose, by its explicit terms, this interpretation is immaterial.

1, 12 (1990); Gordon v. Norton, 322 F.3d 1213, 1216-17 (10th Cir. 2003).[30] Nutraceutical's takings claim is a claim for damages brought pursuant to the Constitution. Accordingly, unless a relevant statute has somehow withdrawn Tucker Act jurisdiction over Nutraceutical's takings claim, its claim cannot be brought in this Court. See Presault, 494 U.S. at 1216-17.

Nothing in DSHEA, the APA, or any other relevant statute affirmatively withdraws Tucker Act jurisdiction over Nutraceutical's takings claim. Therefore, Nutraceutical's claim can be brought only in the Court of Federal Claims and this Court is without jurisdiction to entertain it.

2. EVEN IF THIS COURT HAD JURISDICTION OVER NUTRACEUTICAL'S TAKINGS CLAIM, THE FINAL RULE DOES NOT CONSTITUTE A TAKING

The Takings Clause of the Fifth Amendment provides: "nor shall private property be taken for public use, without just compensation." U.S. Const. amend. V. The Supreme Court has stated that the purpose of the takings clause is "to prevent the government from forcing some people alone to bear public burdens which, in all fairness and justice, should be borne by the public as a whole." Eastern Enterprises v. Apfel, 524 U.S. 498, 522 (1998) (internal quotation omitted).

"A party challenging governmental action as an unconstitutional taking 'bears a substantial burden'" in establishing that a taking has occurred. Pittsburg County Rural Water Dist. No. 7 v. City Of McAlester, 358 F.3d 694, 719 (10th Cir. 2004) (quoting Eastern

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[30] The "Little Tucker Act" creates concurrent jurisdiction for claims against the Federal government that do not exceed $10,000. 28 U.S.C. § 1346.

Enterprises, 524 U.S. at 523). Further, a "'taking' may more readily be found when the interference with property can be characterized as a physical invasion by the government, than when interference arises from some public program adjusting the benefits and burdens of economic life to promote the common good." Penn Cent. Transp. Co. v. City of New York, 438 U.S. 104, 124 (1978) (internal citations omitted). Because Nutraceutical does not allege a physical invasion of its property, its claim is not a "classic taking." Eastern Enterprises, 524 U.S. at 522. Instead, Nutraceutical must rely on the claim of a taking by imposition of a government regulation, whereby if a "regulation goes too far [then] it will be recognized as a taking." Pennsylvania Coal Co. v. Mahon, 260 U.S. 393, 415 (1922).

There are two possible types of takings by regulation - a per se or categorical taking and non-categorical regulatory taking. The taking alleged by Nutraceutical necessarily would be of the second type, and not a categorical taking. A categorical taking by regulation occurs only in the rare circumstance where the regulation "prohibits all 'economically beneficial use'" of a party's property. Clajon Prod. Corp. v. Petera, 70 F.3d 1566, 1577 (10th Cir. 1995) (quoting Lucas v. South Carolina Coastal Council, 505 U.S. 1003, 1014 (1992)); see also Bass Enterprises Prod. Co. v. United States, 381 F.3d 1360, 1365 (Fed. Cir. 2004) (explaining that a categorical taking occurs only in the "extraordinary circumstance" where all productive and economically beneficial use of property is prohibited).

Even though it styles its claim, in part, as a "categorical" taking, Nutraceutical does not allege, nor can it, that the Final Rule deprived it of all economic use of its business or

commercial property. In determining whether there has been a taking, the whole parcel of property at issue is to be considered. Tahoe-Sierra Preservation Council v. Tahoe Regional Planning Agency, 535 U.S. 302, 327 (2002); see also Andrus v. Allard, 444 U.S. 51, 65-66 (1979) (takings analysis involves examination of the whole "bundle" of property rights). Accordingly, it is appropriate to consider Nutraceutical's commercial or business property in the aggregate in determining whether there has been a categorical or per se taking. And, although Nutraceutical can no longer market EDS, it can continue to manufacture and distribute other dietary supplement products and can devote the production capacity previously devoted to EDS to other product lines. The Final Rule, therefore, has not effected a categorical taking of Nutraceutical's property.

Although the Supreme Court has set forth a number of factors to consider in assessing whether a non-categorical regulatory taking has occurred, this analysis boils down to "an examination of the 'justice and fairness' of the governmental action." Eastern Enterprises, 524 U.S. at 523 (explaining that the "justice and fairness" inquiry is, by its nature, "essentially ad hoc and fact intensive"). The factors courts assess when reviewing a non-categorical regulatory taking include the character of the government action, the regulation's interference with reasonable investment-backed expectations, and the economic impact of the regulation. Id.; see also Pittsburg County Rural Water Dist., 358 F.3d at 718 (quoting Eastern Enterprises). Here, the character of the governmental action in the Final Rule and the lack of reasonable investment-

backed expectations weigh so heavily in the government's favor that, as a matter of law, the Final Rule cannot constitute an unconstitutional taking.

FDA promulgated the Final Rule to advance a paramount governmental interest - the health and safety of the public. In promulgating the Final Rule, FDA conducted an extensive review of the scientific evidence relating to EDS and concluded that the benefits associated with these products were extremely minimal and were far outweighed by serious risks of illness and injury. This exercise of regulatory authority is a classic example of the government using its police power to effectuate an important public purpose. Indeed, protecting the health, safety, and welfare of the public repeatedly has been recognized as the type of governmental action that does not involve a taking. See, e.g., Keystone Bituminous Coal Ass'n v. DeBenedicts, 480 U.S. 470, 488 (1987); Penn Cent., 438 U.S. at 125; Rose Acre Farms v. United States, 373 F.3d 1177, 1191-92 (Fed. Cir. 2004); Atlas Corp. v. United States, 895 F.2d 745, 757 (Fed. Cir. 1990).

The character of the government action in these circumstances is sufficient basis alone for the Court to determine that no taking has occurred. The Supreme Court, recognizing that restrictions on uses of property are often necessary for the public good, repeatedly has emphasized that the nature of the government action is "critical" to the takings analysis. See Keystone Bituminous, 480 U.S. at 488-92. Here, the Final Rule's declaration that EDS may not be marketed because they present an unreasonable risk of illness or injury, see 69 Fed. Reg. at 6788, is necessary to effectuate the compelling government purpose of protecting the public

health. This is a legitimate and, indeed, necessary exercise of the government's police power, and simply not the type of action that requires just compensation under the Fifth Amendment.

In any event, Nutraceutical also lacked a reasonable, investment-backed expectation of a static regulatory environment in which FDA would take no action regarding EDS. It is well-established that entities choosing to do business in highly-regulated fields are not entitled to the same expectations regarding the legal and regulatory environment as participants in less-regulated businesses: "Those who do business in the regulated field cannot object if the legislative scheme is buttressed by subsequent amendments to achieve the legislative end." See Connolly v. Pension Benefit Guar. Corp., 475 U.S. 211, 227 (1986) (quoting FHA v. Darlington, Inc., 358 U.S. 84, 91 (1958)); see also Wyoming Hosp. Ass'n v. Harris, 727 F.2d 936, 941 (10th Cir. 1984).

As Nutraceutical was aware, FDA had been considering regulatory restrictions relating to EDS since 1997. Indeed, Nutraceutical repeatedly filed comments regarding proposed regulatory changes since 1997. As described above, Nutraceutical's comments demonstrated that it was aware that FDA might restrict or ban EDS, and any expectation that the regulatory environment would stay the same was unreasonable. Indeed, Nutraceutical was, or should have been, aware long before 1997 that FDA could further regulate EDS. Furthermore, the regulation of dietary supplements was drastically altered in 1994, upon passage of DSHEA. To say that Nutraceutical had reasonable, investment-backed expectations that the regulatory environment would remain static in these circumstances is simply not credible.

The final factor in a regulatory takings analysis is the economic impact of the governmental action. As explained above, the Final Rule has not deprived Nutraceutical of all economically viable use of its property because the only products Nutraceutical is prohibited from marketing are EDS, which pose a threat to the public health. Although Nutraceutical may suffer economic loss as a result of the Final Rule, such loss, standing alone, does not rise to the level of an unconstitutional taking. See, e.g., Mountain States Legal Found. v. Hodel, 799 F.2d 1423, 1429 (10th Cir. 1986) (a government regulation may "'curtail[] some potential for the use or economic exploitation of private property'" without becoming a taking requiring compensation) (quoting Andrus v. Allard, 444 U.S. 51, 62 (1979)). Furthermore, it is reasonable for Nutraceutical to bear any costs imposed by the Final Rule, rather than the public, as Nutraceutical was profiting off the sale of a product that posed a public health risk. This is not a situation where the government is requiring a private party to bear a cost that should properly be borne by the public as a whole, see Eastern Enterprises, 524 U.S. at 522, and hence "fairness and justice" do not require the government to compensate Nutraceutical for any economic impact that Nutraceutical may have to bear as a result of the Final Rule.

The factors relevant to a regulatory taking analysis weigh against Nutraceutical's claim that the Final Rule effects an unconstitutional taking. Nutraceutical is not entitled to any compensation whatsoever from the government.

VI. CONCLUSION

For the foregoing reasons, this Court should deny Nutraceutical's Motion for Summary Judgment and grant Defendants' Cross-Motion for Summary Judgment.

Respectfully submitted,

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Dated: November 4, 2004

CERTIFICATE OF SERVICE

I hereby certify that on this 4th day of November, 2004, I caused to be served by regular mail, postage prepaid, copies of "DEFENDANTS' OPPOSITION TO PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT, AND MEMORANDUM IN SUPPORT OF CROSS-MOTION FOR SUMMARY JUDGMENT" addressed as follows:

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Nutraceutical, et al.

vs.

Crawford, et al.

Exhibits to this document (#15) are extremely oversized (one box filled with unbound papers) and have therefore been placed in the basement as they will not fit on the regular filing shelves. They are not scanned.